

United States Patent and Trademark Office



APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,117	02/27/2002	David W. Morris	529452000121	7176
55255	7590 08/28/2006		EXAM	INER
	ISCOVERY INC.		AEDER,	SEAN E
P.O. BOX 80	TUAL PROPERTY - R440		ART UNIT	PAPER NUMBER
EMERYVIL	LE, CA 94662-8097		1642	
			DATE MAILED: 08/28/2000	6

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)
Office Asticus Occurrences	10/085,117	MORRIS ET AL.
Office Action Summary	Examiner	Art Unit
	Sean E. Aeder, Ph.D.	1642
The MAILING DATE of this communication apperiod for Reply	opears on the cover sheet with the c	correspondence address
A SHORTENED STATUTORY PERIOD FOR REP WHICHEVER IS LONGER, FROM THE MAILING I - Extensions of time may be available under the provisions of 37 CFR 1 after SIX (6) MONTHS from the mailing date of this communication. - If NO period for reply is specified above, the maximum statutatory period - Failure to reply within the set or extended period for reply will, by statu Any reply received by the Office later than three months after the maili earned patent term adjustment. See 37 CFR 1.704(b).	DATE OF THIS COMMUNICATION .136(a). In no event, however, may a reply be tind d will apply and will expire SIX (6) MONTHS from the, cause the application to become ABANDONE	N. nely filed the mailing date of this communication. D (35 U.S.C. § 133).
Status		
1) Responsive to communication(s) filed on 20	March 2006.	
	is action is non-final.	
3) Since this application is in condition for allow	ance except for formal matters, pro	osecution as to the merits is
closed in accordance with the practice under	Ex parte Quayle, 1935 C.D. 11, 49	53 O.G. 213.
Disposition of Claims		
4)⊠ Claim(s) <u>20-31</u> is/are pending in the applicati	on.	
4a) Of the above claim(s) <u>22</u> is/are withdrawn		
5) Claim(s) is/are allowed.		
6)⊠ Claim(s) <u>20,21 and 23-31</u> is/are rejected.		
7) Claim(s) is/are objected to.		
8) Claim(s) are subject to restriction and	or election requirement.	
Application Papers		
9) The specification is objected to by the Examir	ner.	
10) ☐ The drawing(s) filed on is/are: a) ☐ ac	ccepted or b) objected to by the	Examiner.
Applicant may not request that any objection to th	e drawing(s) be held in abeyance. Se	e 37 CFR 1.85(a).
Replacement drawing sheet(s) including the corre	ection is required if the drawing(s) is ob	jected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the E	Examiner. Note the attached Office	Action or form PTO-152.
Priority under 35 U.S.C. § 119		
12) Acknowledgment is made of a claim for foreig a) All b) Some * c) None of:	gn priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:1.☐ Certified copies of the priority docume	nts have been received	
2. Certified copies of the priority document		ion No
3. Copies of the certified copies of the pri		
application from the International Bure	·	
* See the attached detailed Office action for a lis	• • • • • • • • • • • • • • • • • • • •	ed.
Attachment(s)		
1) Notice of References Cited (PTO-892)	4) Interview Summary	
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/0 Paper No(s)/Mail Date 	Paper No(s)/Mail D 5) Notice of Informal F 6) Other: <u>sequence co</u>	Patent Application (PTO-152)

Detailed Action

The Election filed 3/20/06 in response to the Office Action of 6/1/05 is acknowledged and has been entered. Applicant elected group VI and human EGR1 (SEQ ID NO:167) with traverse.

The traversal is on the ground(s) that a search and examination of more than one group would not impose a serious burden on the examiner. Applicant asserts that searching group III (a method of screening drug candidates) together with elected group VI (a method of diagnosing carcinoma or a propensity of carcinoma) would not constitute a serious burden. Applicant argues that the same field of search is appropriate for group III and group VI. Applicant further argues that a search of elected SEQ ID NO:167 would provide results relevant to both group VI and unelected group III. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of groups III and VI are distinct for the reasons set forth in the Office Action. Each group comprises distinct steps, utilizes different products, and differs at least in objectives and criteria for success, which demonstrates that each method has a different mode of operation. Searching and examining both of these methods would result in a serious burden on the examiner. Furthermore, it is noted that the literature search, particularly relevant in this art, is not coextensive and is very important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Art Unit: 1642

Claims 1-19 were pending.

Claims 1-19 were cancelled by Applicant.

Claims 20-31 were newly added by Applicant.

Claim 22 is withdrawn from further consideration by the examiner under 37 CFR

1.142(b) as being drawn to a non-elected invention.

Claims 20, 21, and 23-31 are currently under consideration.

Claim Objections

Claims 20, 21, and 23-31 are objected to for encompassing unelected inventions.

Claims 20, 21, and 23-31 encompass unelected cancer associated (CA) genes and their respective SEQ ID NOs. Further, it is noted that the SEQ ID NO:167 represents the elected invention and is not a species. Proper correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 21, and 24-31 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 and dependent claim 21 are rejected because claim 20 is incomplete for omitting essential steps, such omission amounting to a gap between the steps.

Claim 20 recites a method of detecting cancer wherein detecting some kind of differential expression of a CA gene is indicative of cancer; however, it is unclear what expression of a gene in a patient sample is compared in order to determine a differential expression. Further, it is unclear what kind of differential expression would be indicative of cancer. For example, the claims do not recite whether an increase or a decrease in expression, as compared to some kind of control, is indicative of cancer. Thus, there are missing steps involving comparing and correlating. See MPEP § 2172.01.

Claims 24, 27, and dependent claims 25, 26, and 28-31 are rejected because claims 24 and 27 recite: "...an unaffected individual...". It is unclear what Applicant means by "unaffected". It is unclear what would not have affected said unaffected individual.

Claim 24 and dependant claims 25-26 are rejected because claim 24 recites:

"...a decrease of at least 50% between the level of mRNA in (a) and the level of mRNA in the second or the third sample ...". It is unclear from which sample a decrease in expression would be indicative of cancer or a predisposition to cancer. Further, it is unclear from which sample a measurement is calculated in order to determine how much expression constitutes a 50% decrease. Given the above reasons, the metes and bounds of the claims cannot be determined.

Page 5

Art Unit: 1642

Claim 27 and dependant claims 28-31 are rejected because claim 27 recites:

"...a decrease of at least about 50% between the level of CA gene expression in (a) and the level of CA gene expression in the second or the third sample ...". It is unclear from which sample a decrease in expression would be indicative of cancer or a predisposition to cancer. Further, it is unclear from which sample a measurement is calculated in order to determine how much expression constitutes a 50% decrease.

Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 29 is rejected for reciting: "...wherein the decrease between the level of CA gene expression in (a) and the level of the CA gene expression in the second or third sample ...". It is unclear from which sample a decrease in expression would be indicative of cancer or a predisposition to cancer. Further, it is unclear from which sample a measurement is calculated in order to determine how much expression constitutes a 100% decrease. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 24 recites the limitation "the level of mRNA in (a)". There is insufficient antecedent basis for this limitation in the claim. It is unclear whether "the level of mRNA in (a)" means the level of total mRNA in a first sample, the level of mRNA of a specific (CA) gene having the nucleic acid sequence of SEQ ID NO:167 in said first sample, or

something else. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 24 recites the limitation "a level of the mRNA in a second sample". There is insufficient antecedent basis for this limitation in the claim. It is unclear whether "a level of the mRNA in a second sample" means the level of total mRNA in said second sample, the level of mRNA of a specific (CA) gene having the nucleic acid sequence of SEQ ID NO:167 in said second sample, or something else. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claim 24 recites the limitation "a level of the mRNA in a third sample". There is insufficient antecedent basis for this limitation in the claim. It is unclear whether "a level of the mRNA in a third sample" means the level of total mRNA in said third sample, the level of mRNA of a specific (CA) gene having the nucleic acid sequence of SEQ ID NO:167 in said third sample, or something else. Given the above reasons, the metes and bounds of the claims cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 21, and 23-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosing prostate cancer

Page 7

comprising detecting an increase in Egr-1 gene expression (SEQ ID NO:167) in a prostate tissue sample as compared to Egr-1 gene expression (SEQ ID NO:167) in a normal prostate tissue, does not reasonably provide enablement for a method of diagnosing every other type of cancer comprising detecting just any type of change in expression of just any CA gene in just any type of sample, as compared to any type of control. Further, the specification does not enable any kind of diagnostic assay wherein one would be able to predictably determine whether someone has a predisposition to any cancer by measuring expression of Egr-1 (SEQ ID NO:167) in any sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The instant claims are broadly drawn to a method of diagnosing every type of cancer and methods of determining whether a person has a predisposition for every type of cancer comprising detecting just any type of change in just any CA gene in just any type of sample, as compared to any type of control.

The specification discloses that SEQ ID NO:167 is a cancer associated (CA) nucleic acid (page 10 lines 9-12 and table 29, in particular). The specification further discloses that CA nucleic acids are nucleic acids that were identified through use of oncogenic retroviruses, whose sequences insert into the genome of lymphatic tissue resulting in carcinoma (page 3 lines 17-29 and page 7 lines 20-24, in particular). Further, the specification prophetically states that "oncogenes that are identified in one type of cancer such as lymphoma or leukemia have a strong likelihood of being involved in other types of cancers as well..." (page 3 lines 21-24).

The specification lacks <u>any</u> working example showing that SEQ ID NO:167 is aberrantly expressed in <u>any</u> cancer type. Further, undue experimentation would be required to determine whether the expression level of SEQ ID NO:167 is indicative of every carcinoma or indicative of a predisposition for every cancer. However, the teachings of Eid et al (Cancer Research, 6/1/98, 58:2461-2468) demonstrate that an increase in Egr-1 expression in prostate biopsies from a subject, as compared to Egr-1 expression in normal prostate tissue, is indicative that said subject has prostate cancer (Figure 2, in particular). The prior art does not teach or suggest that methods of measuring Egr-1 (SEQ ID NO:167) expression could be used to determine whether a patient has a predisposition to any kind of tumor with any predictability of success.

The state of the prior art dictates that if a molecule such as a specific polynucleotide, such as that set forth in SEQ ID NO:167, is to be used as a surrogate for a diseased state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed

Art Unit: 1642

polynucleotide to be used in a diagnostic manner. For example, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker (intermediate end point marker) to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Therefore, absent evidence of the polynucleotide's expression including the correlation to a diseased state, one of

Page 9

skill in the art would not be able to predictably use the polynucleotides in any diagnostic setting without undue experimentation.

The level of unpredictability for the detection of any disease and the detection of a predisposition to any disease is quite high. Since neither the specification nor the prior art provide evidence of a universal association between the claimed method and every cancer and every type of sample, a practitioner wishing to practice the claimed invention would be required to provide extensive experimentation to demonstrate such an association. Such experimentation would in itself be inventive.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to a method of diagnosing and determining whether a person has just any type of cancer or has a predisposition for just any type of cancer comprising detecting just any type of change expression in just any CA gene in just any type of sample, as compared to any type of control, and Applicant has not enabled said methods because it has not been shown that detecting every type of differential expression of every type of CA gene, as compared to every type of control, in every type of sample, could predictably be used as a universal method to determine whether a person has just any type of cancer or is predisposed to having any type of cancer.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 21, 24-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Eid et al (Cancer Research 58, 2461-2468) as evidenced by Monia et al (US Patent 6,008,048; 12/28/99).

Claim 20 is drawn to a method of diagnosing cancer in a patient comprising detecting the presence of differential expression of a polynucleotide that has the nucleotide sequence set forth in SEQ ID NO:167 in a patient sample, wherein the presence of differential expression of the nucleotide sequence set forth in SEQ ID NO:167 in said sample is indicative of a patient who has cancer. Claim 21 is drawn to the method of claim 20 wherein the cancer is prostate cancer. Claim 24 is drawn to a method of diagnosing cancer comprising (a) measuring a level of mRNA of a polynucleotide that has the nucleotide sequence set forth in SEQ ID NO:167 in a first sample, said first sample comprising a first tissue type of a first individual, and (b) comparing the level of mRNA in (a) to (1) a level of mRNA in a second sample, said second sample comprising a normal tissue type of said first individual, or (2) a level of the mRNA in a third sample, said third sample comprising a normal tissue type from an unaffected individual, wherein a decrease of at least 50% between the level of mRNA in

(a) and the level of the mRNA in the second sample or the third sample indicates that the first individual has cancer. Claim 25 is drawn to method of claim 25 wherein the mRNA has the nucleotide sequence of SEQ ID NO:167. Claim 26 is drawn to the method of claim 24, wherein the cancer is prostate. Claim 27 is drawn to a method of diagnosing cancer comprising (a) measuring a level of the nucleotide sequence set forth in SEQ ID NO:167 in a first sample, said first sample comprising a first tissue type of a first individual and (b) comparing the level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in (a) to (1) a level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in a second sample, said second sample comprising a normal tissue type of said first individual or (2) a level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in a third sample, said third sample comprising a normal tissue type from an unaffected individual, wherein a decrease of at least about 50% between the level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in (a) and the level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in the second sample or third sample indicates that the first individual has cancer. Claim 28 is drawn to the method of claim 27 wherein the cancer is prostate cancer. Claim 29 is drawn to the method of claim 24 or 27 wherein the decrease between the level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in (a) and the level of expression of the nucleotide sequence set forth in SEQ ID NO:167 in the second sample or the third sample is 100%. Claim 30 is drawn to the method of claim 27, wherein the level of expression of the nucleotide sequence set forth

in SEQ ID NO:167 is determined by measuring mRNA levels. Claim 31 is drawn to the method of claim 30 wherein the mRNA has the sequence of SEQ ID NO:167.

Eid et al teaches a method of diagnosing prostate cancer in a patient comprising detecting the presence of differential expression of Egr-1 in a patient sample, wherein the presence of differential expression of Egr-1 in said sample, as compared to Egr-1 expression in a control sample, indicates a patient has prostate cancer (Figure 2, in particular). As evidenced by Monia et al, SEQ ID NO:167 is Egr-1 (see attached sequence comparison of SEQ ID NO:47 taught by Monia et al and instant SEQ ID NO:167, in particular). Eid et al further teaches that "normal" control samples are prostate tissues from autopsies of young organ donors and non-malignant prostate tissues form patients that underwent a prostatectomy (page 2461 right column, in particular). Eid et al further teaches a method wherein a decrease of at least 50% between the level of Egr-1 mRNA in a first sample, said first sample comprising a first tissue type of a first individual, and the level of Egr-1 mRNA in said control samples indicates that said first sample was obtained from a patient with prostate cancer (see Figure 2, in particular). Eid et al further teaches a decrease of 100% between the level of Egr-1 mRNA in said first sample and the level of the Egr-1 mRNA in said control samples.

Summary

No claim is allowed. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, but free of the prior art teaching a method of diagnosing cancer comprising detecting

Art Unit: 1642

the presence of differential expression of a gene having the polynucleotide sequence of SEQ ID NO:167 in a patient sample, wherein downregulation of the polynucleotide having the sequence of SEQ ID NO:167 in a patient sample, as compared to a control, is indicative of cancer. The closest prior art for claim 23 is Eid et al (Cancer Research 58, 2461-2468), which teaches a method of diagnosing cancer comprising detecting the presence of differential expression of a gene having the polynucleotide sequence of SEQ ID NO:167 in a patient sample, wherein *upregulation* of the polynucleotide having the sequence of SEQ ID NO:167 in a patient sample, as compared to a control, is indicative of cancer; however, this reference does not teach or suggest a method of diagnosing cancer comprising detecting the presence of differential expression of a gene having the polynucleotide sequence of SEQ ID NO:167 in a patient sample, wherein *downregulation* of the polynucleotide having the sequence of SEQ ID NO:167 in a patient sample, in a patient sample, as compared to a control, is indicative of cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Application/Control Number: 10/085,117 Page 15

Art Unit: 1642

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

SUPERVISORY PATENT EXAMINER

ક

Db 421 GCCGCCGGGGCCCCCAGAGGCGCCAGCAACAGCAGCAGCA	Db 541 (ACACGGGGGAGCCTACGAGCCTGGGAGTGTTTTTTTTTT	OY 661 ATCACCTATACTGGCCGCTTTTCCCTGGAGCCTGCACCACGGCGAACACCTTGTGG 720	721 CCCGAGCCCTCTTCAGCTTGGTCAGTGGCCTAGTGAGCATGACCAACCCACGGCCTCC 781 TCGTCCTCAGCACCATCTCCAGCGCCTCCTCGCCTCCGCCTCCGCTTCCGCTTCCGCTTCGCCTTCCGGCTTCCGTTCCTTCCGTTCCTTCCGCTTCCTTCCGCTTCCTTCCGCTTCCTTCCGCTTCTTCTTTCTTTCTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTT		Db 901 AGGCGBACACTGACACTTTCCCAGAGCCACAAGGCCTCCGGGCTGGGCAGGG 960 QY 961 ACAGCGCTCCAGTACCCGCCTGCTGCCTGCCGCCAAGGGTGCTTCCAGGTTCC 1020 Db 961 ACAGCGCTCCAGTACCCGCTGCTGCTTCCTGCCGCCAAGGGTGCTTCCAGGTTCC 1020 961 ACAGCGCTCCAGTACCCGCGTCCTGCCCTCCCGCCAAGGGTGGCTTCCAGGTTCCC 1020	ON 1021 ATGATCCCCGACTACCTGATACCACAGCAGGGGATCTGGGCCTGGGCCCCCAGAC 1080	1081 CAGAAGCCCTTCCAGGGCCTGGAGAGCCGCAGCAGCAGCCTTCGCTAACCCCTCTGTCT	OY 1141 ACTATTAAGGCTTTGCCACTCGAGGGCGCCCAGGAGGCCCTCAATACCAGC 1200 Db 1141 ACTATTAAGGCTTTGCCACTCAGTCGGGCTCCCAGGAGCCCTCAATACCAGC 1200 ON 1201 TACCAGTCCAAGACTCAGTCAGAGCCAGGACCTCGAAGGCCTCAATACCAGC 1200	1261 AGCCCCCCACACAAACCCTTACCAGTCAGTCAGTCATCATCATCACCAGCAAGTTCTCCAACTTCACCAAGTATCACCAAGTATCACCAAGTATCACCAAGTCATCACCAAGTCATCATCATCACTACACTCAGTCAAGTCAAGTCATCATCATCACCAAGTCAAG	1261 ACGCCCACGACGCCTTACGCTTGCCAGTGGAGTCCTGTGATCGCCGCTTCTCC 1321 CGCTCCACGAGGTCACCCGCCACATCGCATACACACAGAAGCCTATCCAGTGC	1321 CGFTCGGACGTCACCGGCCACATCCGCATCGACACAGAGGCCTTCCAGTGC 1381 GCPTGGAGGGGGAAGGCCGACATCGACGACGACGAGAGGCCTTCCAGTGC	1381/ CGC#TCTGCATGCGCAACTTCAGCCGCGCGACCACCTCCACCCAC	7441 AGGCGAAAAGCCCTTCGCCTGCGACATCTGTGGAAGAAGTTTGCCAGGAGCGATGAA	OY 1501 GCCAAGAGGTACCAAGATCCACTTGCGGCAGAAGGAAGGA
	3121 GCTGCGATTGGG 3132 SULT 3 -09-300-958A-32	Sequence 32, Application US/09300958A Patent No. 6495319 GENERAL INFORMATION APPLICANT: MCClelland, Michael APPLICANT: Welsh, John	APPLICANT: Trenkle, Thomas TITLE OF INVENTION: Reduced Complexity Nucleic Acid Targets and Methods of TITLE OF INVENTION: Welling Same FILE REPERENCE: P-PH\3457 CURRENT APPLICATION NUMBER: US/09/300,958A CURRENT FILING DATE: \\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	LING DATE: 1998, 00. LICATION NUMBER: LICATION NUMBER: LICATION NUMBER: LING DATE: 1999-02 SEQ ID NOS: 85	SSO ID NO 32 LENGTH: 3132 TYPE: DNA ORGANISM: Homo sapiens	Query Match Best Local Similarity 100.0%; Score 3132; DB 3; Length 3132; Best Local Similarity 100.0%; Pred No 9; Matches 3132; Conservative 0; Migmacches 0; Indels 0; Gaps 0;	TTGGGAGCGCCGCCGCCGCCGCCGCAGCTTCCGCCGCCGCA 60	61 GGACCGGCCCTGCCCCAGCTCCGGGGGGGGGGGCCCGCCC	GCGAGTCGCGCCCCCCTCGAGCGCTTCTCAGTGTTCCCCGCGCCCCGCATGTA 	181 GCCAGGCCCGGCAACGGTGTCCCTGCAGGTCCAGGCTGCAGGCTGCACCCCCCGGCCCC 240	241 GACACCAGCTCTCCÁG/CTGCTCGAGGATGGCGGGGGAAGGGCGAGGAGTGCAGGTG 300 	301 AIGTCCCGCGGGAATCICTGACCGTTCGGATCCTTTCCTCACCCACCATGGAC 360	361 AACTACCGFAAGCTGGAGGAGGATGATGCTGCTGAGCAACGGGGCTCCCCAGTTCCTCGGC 420	421 GCGCCGGGGGCCCCAGAGGGCAGCAGCAGCAGCAGCAGCA

음 중 음

```
-
                                                                                                                                                                61
                                                                                                                                                                                                                          181
                                                                                                                                                                                                                                                       241
                                                                                                                                                                               61
                                                                                                                                                                                                                                                                                    301
                                                                                                                                                                                                                                                                                                                 361
                                                                                                                                                                                                                                                                                                                                                                                                        541
                                                                                                                                                                                                                                                                                                                                             421
                                                                                                                                                                                                                                                                                                                                                                                                                                                   601
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 661
                                                                                                                                  ò
                                                                                                                                               셤
                                                                                                                                                               à
                                                                                                                                                                         셤
                                                                                                                                                                                           Š
                                                                                                                                                                                                        ద
                                                                                                                                                                                                                                     g
                                                                                                                                                                                                                         8
                                                                                                                                                                                                                                                     δ
                                                                                                                                                                                                                                                                   셤
                                                                                                                                                                                                                                                                                   ò
                                                                                                                                                                                                                                                                                              d
                                                                                                                                                                                                                                                                                                               ઠ
                                                                                                                                                                                                                                                                                                                            쉽
                                                                                                                                                                                                                                                                                                                                          ઠે
                                                                                                                                                                                                                                                                                                                                                        셤
                                                                                                                                                                                                                                                                                                                                                                         ઠે
                                                                                                                                                                                                                                                                                                                                                                                     a
                                                                                                                                                                                                                                                                                                                                                                                                     ò
                                                                                                                                                                                                                                                                                                                                                                                                                    셤
                                                                                                                                                                                                                                                                                                                                                                                                                                    Š
                                                                                                                                                                                                                                                                                                                                                                                                                                                 셤
                                                                                                                                                                                                                                                                                                                                                                                                                                                                à
                                                                                                                                                                                                                                                                                                                                                                                                                                                                              g
      2280
                    2280
                                  2340
                                                               2400
                                                                             2400
                                                                                            2460
                                                                                                           2460
                                                                                                                         2520
                                                                                                                                       2520
                                                                                                                                                                                   2640
                                                                                                                                                                                                  2640
                                                                                                                                                                     2580
                                                                                                                                                                                                                 2700
                                                                                                                                                                                                                               2700
                                                                                                                                                    TACTGCTTGACCGTACTCTCACA 2580
                                                                                                                                                                                                                                              2760
                                                                                                                                                                                                                                                            2760
                                                                                                                                                                                                                                                                           2820
                                                                                                                                                                                                                                                                                2940
                                                                                                                                                                                                                                                                                                     ATCTGAACTCTCAAAGTCTATTTTTTAA 2880
                                                                                                                                                                                                                                                                                                                                           PATTATTTGTGGTTCTATTTACT 3000
                                                                                                                                                                                                                                                                                                                                                                                            TATAAACACATTGAATGCGCT 3060
                                                                                                                                                                                                                                                                                                                                                                                                             3060
                                                                                                                                                                                                                                                                                                                                                                                                                        AAATTAAAACGAAAATAAAGTA 3120
                                                                                                                                                                                                                                                                                                                                                                                3000
 GACCCCTTGCTCCCTTCAATGCTAGAAATCGAGTTGGCAAAATGGGGGTTTGGGCCCCTC
           2221 GACCCCTTGCTCCCTTCAATGCTAGAAATCGAGTTGGCAAATGGGGTTTGGGCCCCCC
                             TAGGTCCTCACT
                                                                             GTTAGGTCCTCACT
                                                                                           CTATTTTGTGATGA
                                                                                                         rccrcrarrrrardrarda
                                                                                                                       GTCCCAGTATTCTCAGAGC
                                                                                                                                   rdaktoritititifakaktaktatototakaratitorokakt
                                                                                                                                                               petraaccytrigiyataciecrigaccetacicaca
                                                                                                                                                                                 CACCTCTAGCCTTAAGGGGGGCAGGGAGTGATG
                                                                                                                                                                                                               CTTTTGTGTGATGCCCCTTGCTGATGGCTT
                                                                                                                                                                                                                             Gccriritaticidalicacicitaticali
                                                                                                                                                                                                                                           CACCTCTAGCCTTAAGGGGGGCAGGGAGTGATG
                                                                                                                                                                                                                                                                        AGGAAGAGGCTGAGCTGAGCTTCGGTTCTCC
                                                                                                                                                                                                                                                                                                                                                                                                                                 TGGAATGTTGTAGTTACCTACTGAGT
                                                                                                                                                                                                                                                                                                                                                                          TATTTGTGGTTCTATTTTACT
                                                                                                                                                                                                                                                                                                                                                                                                           GCTTATAAACACATTGAATGCGCT
                                                                                                       AAAAAAAGCCAAGCAAACCAAyGGTGA
                                                                  AAAAAAAAGCCAAGCAAACCAATGG
                                                                                                                                                                                                                                                                                                                                                                                                                                 ATGGGATATGTGGTGTATATCCTTCCAAA
                                                                                                                                                                                                                                                                                                                                                                                                                       TGGGATATGTGGTGTATATCCTTCCAA
                                                                                                                                                                                                                                                                                                                                                                                                   # TTTGCTTAAACAAGTGACTGTTTT
                                                                                                                                                                                                                                                                                                                                                                      TIMETATETATEAACATECAG
                                                                                                                                                                                                                                                                                                                                              creananteraphriparantaratreagg
                                                                                                                                                                                                                                                                                                                                                              TATGTTATGAACATGC
                                                                                                                                                                                                                                                                                                                 2821 AGAATGTAAGAAAAGAAAATCTAAAACAAA
                                                                                                                                                                                                                                                                                                                                  AAATATATTCAGG
                                                                                                                                                                                                                                                                                                     MATCIABABCAA
                                                                                                                                                    CCCTTAACCTT
                                                                                                                                                                                                                                                                                      GGGAGGAAATA
                                                                                                                                                                                                              TTTGGTTTAAAAAGTTTCACGTO
                                                                                                                                                                                                                            TTTGGTTTAAAAAGTTTCACG;
                                                                                                                                                                                        GACATGTGCAATTGTGAGGGA
                                                                                                                                                                                TGTGGCAAAATATGGTTTGG
                                                                                                                                                                2521 Argigicadagigirging
                                                                                                                                                                                                                                                       2701 GACATGTGCAATTGTGAGG
                                                                                                                                                 2521 ATGTGTCAGAGTGTTGT
                                                                                                                             TGCTGTGACAATAAGT
                                                                                                                                                                                                                                                                                                                                                                                                                                                     GCTGGGATTGGG 3132
                                                                                                                                                                                                                                                                                                                                                                                                                                                                    SATTGGG 3132
                                                                                                                    TGCTGTGACAATAAG
                                                                                                                                                                                                                                                                                                   AGAATGTAAGAAAAQ
                                                                                                     2401 TGGGGGAAAAAA
                                                                                                                                                                                                                                                                                    2761 ATTTGGGGGAGGCT
                                                                                      TGGGGGAAAAAA
                                                                                                                                                                                                                                                                                                                                 CTGAAAATGTAAA
                                            2281 AGAGCCCTGC
                                                                                                                                                                                                                                                                                                                                                             AGGCGGCGAT
                                                                                                                                                                                                                                                                                                                                                                                          TTGTACT
                                                                                                                                                                                                                                                                                                                                                                                                                       TTATTÉ
2221
                                                          2341
                                                                        2341
                                                                                      2401
                              2281
                                                                                                                    2461
                                                                                                                                                                                                           2641
                                                                                                                                   2461
                                                                                                                                                                                2581
                                                                                                                                                                                             2581
                                                                                                                                                                                                                           2641
                                                                                                                                                                                                                                          2701
                                                                                                                                                                                                                                                                      2761
                                                                                                                                                                                                                                                                                                   2821
                                                                                                                                                                                                                                                                                                                                2881
                                                                                                                                                                                                                                                                                                                                              2881
                                                                                                                                                                                                                                                                                                                                                                                                                       3061
                                                                                                                                                                                                                                                                                                                                                                                                                                     3061
                                                                                                                                                                                                                                                                                                                                                                                          3001
                                                                                                                                                                                                                                                                                                                                                                                                        3001
                                                                                                                                                                                                                                                                                                                                                                                                                                                    3121
                                                                                                                                                                                                                                                                                                                                                             2941
                                                                                                                                                                                                                                                                                                                                                                           2941
                                                                                                                                                                                                                                                                                                                                                                                                                                                                  3121
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         RESULT 2
ò
             셤
                                          윱
                           δ
                                                         ઠે
                                                                     셤
                                                                                      ò
                                                                                                  g
                                                                                                                   à
                                                                                                                             셤
                                                                                                                                            Š
                                                                                                                                                             셤
                                                                                                                                                                               Š
                                                                                                                                                                                          윤
                                                                                                                                                                                                           Š
                                                                                                                                                                                                                         셤
                                                                                                                                                                                                                                                   a
                                                                                                                                                                                                                                        ò
                                                                                                                                                                                                                                                                    ઠે
                                                                                                                                                                                                                                                                                셤
                                                                                                                                                                                                                                                                                                 ò
                                                                                                                                                                                                                                                                                                               셤
                                                                                                                                                                                                                                                                                                                              Š
                                                                                                                                                                                                                                                                                                                                           셤
                                                                                                                                                                                                                                                                                                                                                            ò
                                                                                                                                                                                                                                                                                                                                                                         셤
                                                                                                                                                                                                                                                                                                                                                                                                     g
                                                                                                                                                                                                                                                                                                                                                                                                                                    유
                                                                                                                                                                                                                                                                                                                                                                                         ò
                                                                                                                                                                                                                                                                                                                                                                                                                      ò
                                                                                                                                                                                                                                                                                                                                                                                                                                                    ठ
                                                                                                                                                                                                                                                                                                                                                                                                                                                              엄
```

Sequence 1, Application US/09205921A Patent No. 6008048 GENERAL INFORMATION: APPLICANT: Brett P. Monia APPLICANT: ex M. COWSERT

US-09-205-921-1

ö 120 240 120 180 180 GACACCAGCTCTCCAGCTCGTCCAGGATGGCCGGCCAAAGGCCGAGATGCAGCTG 300 9 360 301 ATGECCCGCTGCAGATCTCTGACCGTTCGGATCCTTTCCTCACCACGCCACCATGGAC 360 420 420 480 480 540 540 9 9 99 99 720 720 780 840 840 780 CGGAGAAACTTGGGGAGCGGCGCGCGCATCGGCGCGCGCAGGCCAGGCTTCGGCCGCGCA GCCAGGCCCCCGCAACGGTGTCCCCTGCAGCTCCAGCCCCGGGGTGCACCCCCCGGCCCC 1 CCGCAGAACTIGGGGAGCCGCCGCCATCCGCCGCCGCAGCTTCCGCCGCCGCA ATGTCCCCGCTGCAGATCTCTGACCCGTTCGGATCCTTTCCTCACTCGCCCACCATGGAC GACACGGGGGAGCACCTACGAGCACCTGACCGCAGAGTCTTTTCCTGACATCTCTCTG AACTACCCTAAGCTGGAGGAGGATGATGCTGCTGCTGAACGGGGCTCCCCAGTTCCTCGGC Gaps 601 AACAACGAGAAGGIGCIGGIGGAGACCAGITACCCCAGCCAAACCACTCGACTGCCCCC CCCGAGCCCCTCTTCAGCTTGGTCAGTGGCCTTAGTGAGCATGACCAACCCACCGGCCTCC TGTCCTCAGCACCATCTCCAGGGCCTCCTCCGCCTCCCCAGAGCCCACCCTG Grag 661 ATCACCTATACTGGCCGCTTTTCCCTGGAGCCTGCACCCAACAGTGGCAACACTT ö ; TITLE OF INVENTION: ANTISENSE MODULATION OF EGR-1 EXPRESSION
; FILE REPERENCE: RTS-0028
; CURRENT APPLICATION NUMBER: US/09/205,921A
; CURRENT FILING DATE: 1998-12-04
; NUMBER OF SEQ ID NOS: 47
; SEQ ID NO 1
; LENGTH: 3132
; TYPE: DNA
; ORGANISM: Homo sapiens
; FRATURE:
; NAME/KEY: CDS
; LOCATION: (271)..(1902)
US-09-205-921-1 Length 3132 Indels DB 3; ö 100.0%; Score 3132; 100.0%; Pred. No. 0; ive 0; Mismatches Query Match 100. Best Local Similarity 100. Matches 3132; Conservative 721 721 781 781 ò 셤 ઠે

. <i>ह</i> े	£.	<i>&</i>	1921 GGGAAAAAGGGAAAAAAGAAACACAAGAGACTTAAAGGACAGGAGGAGGAGGACCATA 1980
q	841 AGCTGCGCAGTGCCATCCAACGACAGCGAGTCCCATTACTCAGCGGCACCCACC	음 &	GGGAAAAGGGAGAAAAGAAACACAAGAGACTTAAAGGACAGGAGGAGGAGAGCATGGCCATA 198
충 음	901 ACGCCGAACACTGACATTTTCCCTGAGCCAAAGCCAAGGCCTTCCCGGGCTCGGCAGGG 960	3 A	1981 GGAGAGGAGGGTTCCTCTTAGGTCGAGATCTCTCAGAGCCAAGTCCTCCTCTA 2040
<i>8</i> €	71 0 0 0	& 43	2041 CTGGAGTGGAAGGTCTATTGGCCAACAATCCTTTCTGCCCACTTCCCCTTCCCCAATTAC 2100
B 성 I	# TOTAL CONTROLL OF THE CONTRO	<i>ò</i> a	2101 TATTCCTTTGACTTCAGCTGCAGAACAGCCATGTCCAAGTTCTTCACCTCTATCCAA 2160
රු සි	GTCT 	λ q	2161 AGAACTIGATTIGCATGGATTITGGATAAATCATTICAGTATCATCTCCATCATATGCCT 2220
& g	CAGC	ራ ብ	2221 GACCCCTTGCTCCCTTCAATGCTAGAAATCGAGTTGGCAAAATGGGGTTTGGGCCCCTC 2280
ර සි	TACCAGTCCCAGCTCATCAAACCCAGCGCATGCGCAAGTATCCCCAACCGGCCCAGCAAG	& 43	2281 AGAGCCTGCCTGCACCTTGTACAGTGTCTGTGCCATGGATTTCGTTTTCTTGGGGT 2340 [
ඊ සි		~ 60 €	2341 ACTCTTGATGTGAAGATAATTTGCATATTCTATTGTATTATTTGGAGTTAGGTCCTCACT 2400 2341 ACTCTTGATGTGAAGATAATTTGCATATTCTATTGTATTTTGGAGTTAGGTCCTCACT 2400
8 3	CGCTCCGACGAGCTCACCCGCCACCCACCACAGCCAGAAGCCCTTCCAGTGC	& g	2401 TGGGGGAAAAAAAAAAAAAGCCAAGCAAACCAATGGTGATCCTCTATTTTGTGATGA 2460
දු පු	CGCATCTGCATGGGGAACTTCAGCGGAGGGACCACCTCACCACCACCACCACCCAC	රු සි	2461 IGCTGTGACAATAAGTTTGAACCTTTTTTTTTGAAACAGCAGTCCCAGTATTCTCAGAGC 2520
& a	ACAGGCGAAAAGCCCTTCGCCTGCGACATCTGTGGAAAGAAA	ý da	2521 AIGIGICAGAGIGIIGIICCGTIAACCTITITGIAAAIACTGCTIGACGIACTCICCACA 2580
& A	CGCBAGAGGGATACCBAGATCCACTTGGGGCAGAAGGACAAGAAAGGAGACAAAAGTGTT CGCBAGAGGGATACCBAGATCCACTTGGGGCAGAAAGGAAAAGAAAA	& g	2581 IGTGGCAAAATATGGTTTTGTTTTTTTTTTTTTAAAAGTGTTTTTT
් ර සි	GTGGCCTCTTCGGCCACCTCCTCTCCTACCGTCCCGGTTGCTACCTCTTAC 162	& a	2641 TITGGITIAAAAGITICACGICTIGGIGCCITITIGIGAIGCCCCTIGCTGAIGGCIT 2700
<i>8</i> 8	COGTCCCCGGTTACTACCTCTTATCCACCCCGGCCACCACCTCATACCCATCCCTGTG 168	ζς d	2701 GACATGCAATTGTGAGGGACATGCTCACCTCTAGCCTTAAGGGGGGCAGGGAGTGATG 2760
දු ද		<i>&</i> 8	2761 ATTTGGGGGAGGCTTTGGGAGCAAATAAGGAAGGCCTGAGCTGAGCTGCGTTCTCC 2820
රු සි	CCCTCCCGGTCGGTCGCCACCACGTACTCCTCTGTTCCCCCTGCTTTCCCGGCCCAGGTCCCCTGCTTTCCCGGCCCAGGTCCCCTCTGTTCCCCCTGCTTTCCCGGCCCAGGTC	<i>ò</i> 8	2821 AGAATGTAAGAAAACAAAATCTAAAAACAAAATCTGAACTCTCAAAAGTCTATTTTTTAA 2880
8		<i>&</i> 4	2881 CTGAAAATGTAAATTTATAAATATATTCAGGAGTTGGAATGTTGTAGTTACCTACTGAGT 2940
		රු සි	2941 AGGCGCCATTTTTGTATGTATGAACATGCAGTTCATTATTTTGTGGTTCTATTTTACT 3000 1941 AGGCGGCGATTTTTGTATGTTATGAACATGCAGTTCATTATTTTGTGGTTCTATTTACT 3000
		<i>&</i> _	3001 TIGIACTIGIGITIGCTTAAACAAAGIGACTGITIGGCTTAIAAACACAITGAAIGCGCT 3060